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# **A Dynamic-Dose Dispensing System for Immediate and Extended Release 3D Printed Tablets**

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## **Abstract**

## 1. Introduction

The prescriptions containing personalised doses of medicines are of utmost importance as they are not prepared commercially by mass production. In the United States, 30 million prescriptions are prepared annually by 3000 compounding pharmacies (website, 2014). A study suggests the most common therapeutic problems, 76% combination not commercially and 43.6% strengths were commercially unavailable (Martin et al., 2009). It is of significant importance to develop a dynamic dispensing system that can respond to different patient's needs rapidly and effectively.

For a preparation method to perfectly suit the demands of personalised method, a safe easily adjustable dispensing station should be created. The station can be operated via a simple user interface with minimal training and can be connected to a wider healthcare network (Skowrya et al., 2015). Clearly, such criteria cannot be fulfilled by conventional tableting methods, where multiple processing stages, large batches, use of costly facilities and experienced labour are common practice (Khaled et al., 2014). Tailoring such system for an individual patient who continuously needs to change his/her medicines dose is too expensive and impractical.

The use of 3D printing as a flexible alternative technique to conventional tableting techniques started with the use of powder-based printing (Katstra et al., 2000; Yu et al., 2009; Yu et al., 2007) (Ursan et al., 2013). Other printing techniques such as inkjet printing (Gu et al., 2012), thermal inkjet printing (Buanz et al., 2011), piezoelectric inkjet printing system (Lee et al., 2012), stereolithography (Melchels et al., 2010) and syringe/extrusion 3D printing (Rattanakit et al., 2012) has also been investigated.

Fused deposition modelling (FDM) is a widely used and affordable bench top 3D printing technique (Lim, 2010). AN FDM based 3D printer uses a pre-prepared polymeric filament e.g. Poly Vinyl Alcohol (PVA) and guide it to pass through a heated nozzle to be extruded at a semi-solid state into fused 3D structure in a layer-by-layer fashion. The potential of FMD based 3D printers to incorporate drug molecules have been previously using commercially available PVA filaments (Masood, 2007) (Goyanes et al., 2014a; Goyanes et al., 2014b). Our research group showed the potential of this printing technology to provide a mini-dispensing dose controlling station via manipulating the volume of the printed design

through input on software (Skowrya et al., 2015). However, the previous attempts suffered several limitations such as limited encapsulation efficiency (<2.5%), the use of non-pharmaceutical grade ingredients, simplistic tablet designs, the use of high temperature and were confined to extended drug release systems (Goyanes et al., 2014a; Goyanes et al., 2014b; Sandler et al., 2014; Skowrya et al., 2015).

In this work, we present a combined approach of manufacturing 3D printed tablet based on FDM 3D printing and hot melt extrusion (HME). We explored the potential of this approach to accurately control the dose and *in vitro* release pattern of a model drug using a number of immediate and extended release polymers. The study was carried out using a realistic drug loading and a challenging capsule-shaped tablet design.

## **2. Materials and methods**

### **2.1. Materials**

Theophylline was purchased from Arcos (UK). Eudragit® RL100 and Eudragit® RS100 formulation were donated by Evonik Industries (Darmstadt, Germany). Hydroxypropyl cellulose SSL grade was donated by Nisso Chemical Europe GmbH (Dusseldorf, Germany). Triethyl citrate (TEC) and triacetin were supplied by Sigma-Aldrich (UK). Scotch blue painter's tape 50 mm was supplied by 3M (Bracknell, UK).

### **2.2. Preparation of theophylline loaded filaments via hot-melt extrusion**

MakerBot Replicator® 2X Experimental 3D Printer (MakerBot Industries, LLC, New York, USA) was utilized to print theophylline tablets. In order to obtain the new formulation hot melt extrusion method was implemented using Thermo Scientific HAAKE MiniCTW (Karlsruhe, Germany).

The compositions and the ratio of drug, polymer plasticizer mixtures are shown in Table 1. About 6g of total blend were carefully weighed and added gradually to counter flow twin screw extruder. The molten mass was allowed to mix for at least 5min to allow homogeneous distribution of drug and polymer within the matrix. The molten mass was then extruded through a die nozzle with cylindrical shape with appropriate diameters. Sample was fed manually using a funnel into the inlet of the extruder setting under feeding temperature as specified in Table 1 and speed of 80 rpm. Mixing temperature was set

between 110-120°C and speed of 50 rpm. Filament was extruded using control torque of 0.6 Nm. The choice of a plasticizer for each filament was determined by literature recommendations. Filaments were stored in sealed plastic bags at room temperature before 3D printing.

### **2.3. Tablet design and printing process**

Blank and theophylline loaded tablets were designed in prolonged typical capsule shape using Autodesk® 3ds Max® Design 2012 software version 14.0 (Autodesk, Inc., USA) and saved in STL format (Figs.1). The design was imported to the 3D printer's software, MakerWare Version 2.4.0.17 (Makerbot Industries, LLC., USA) (Fig.1). A series of tablets with increasing volumes were printed by modifying the dimensions of the design: length x width x heights (L, H, W) without altering the ratios between these dimensions.

### **2.4. Modification of 3D printer**

A MakerBot Replicator® 2X Experimental 3D Printer (MakerBot Industries, New York, USA) was utilized to print Eudragit RL tablets. Tablets were printed using modified settings of the software for PLA filament as follows: type of printer: Replicator 2X; type of filament: PLA; resolution: standard; temperature of building plate: 20 °C; speed of extruder 90 mm/s while extruding and 150 mm/s while traveling; infill: 100%; height of the layer: 200 µm. No supports or rafts were utilized in the printed model.

The following modifications were implemented:

- i) Kapton tape layer (default) provided poor adhesion of the designs to the built plate. Blue Scotch painter's tape was applied to the surface of the printing board to improve adhesion to the surface layer.
- ii) Changing extruder temperature during printing as specified in Table 1 was essential to maintain constant flow of theophylline loaded filaments.

In order to study the impact of infill percentage on drug release from HPC based tablets, infill percentage was varied to 10, 20, 40, 60, 80 and 100%. The impact of printing speed was assessed by modifying the printing resolution low, standard and high while printing 250 mg theophylline tablet.

### **2.5. Determination of drug content**

In order to assess theophylline content in the printed tablets, each tablet was weighed and sonicated in 1000 ml volumetric flask containing 0.1 M HCl. The sonication period were extended to 8 hours to ensure complete drug extraction. Theophylline drug concentration was determined via spectrophotometry (Jenway, Japan) at absorbance  $\lambda_{\text{max}}$  of 272 nm. For higher concentrations, the solution was diluted as suitable with 0.1 M HCl.

### **2.6. Scanning Electron Microscopy**

The surface morphology of the printed tablet was assessed using a Quanta-200 SEM microscope at 20 kV. Samples were placed on metallic stubs and gold coated under vacuum for 2 min using JFC-1200 Fine Coater (Jeol, Tokyo, Japan), prior to imaging.

### **2.7. X-Ray Powder Diffraction**

A powder X-ray diffractometer, D2 Phaser with Lynxeye (Bruker, Germany) was used to assess the crystallinity of theophylline in the drug loaded tablets. Samples were scanned from  $2\theta$  ( $2\theta$ ) =  $5^\circ$  to  $50^\circ$  using  $0.01^\circ$  step width and a 1 second time count. The divergence slit was 1mm and the scatter slit 0.6mm. The wavelength of the X-ray was 0.154 nm using Cu source. The voltage used was 30kV. Filament emission was 10 mA. Using a scan type coupled with a two theta/theta scintillation counter over 30 min.

### **2.8. Differential Scanning Calorimetry (DSC)**

A differential scanning calorimeter DSC Q2000 (TA Instruments, Elstree, Hertfordshire, UK) was utilized to perform thermal analysis. Samples of approximately 5 mg were accurately weighed and placed in a 40  $\mu\text{L}$  standard aluminium pan DSC analysis. Analysis was carried on under a nitrogen environment (50 mL/min). In order to exclude the effect of humidity and to get a clearer  $T_g$ , samples were cooled to  $-10^\circ\text{C}$ , then heated to  $100^\circ\text{C}$ . The temperature was kept isothermal for 5 min then cooled to  $-20^\circ\text{C}$  and left for 2 minutes. The heating and cooling of the samples were performed at of  $10^\circ\text{C}/\text{min}$ . This was followed by a heat scan from  $-20^\circ\text{C}$  to  $300^\circ\text{C}$  at the same rate. All measurements were carried out in triplicates. The data was analyzed using TA 2000 analysis software.

All the samples were subjected to a cycle of heat/cool/heat in order to ensure accurate reading and drying of the polymeric matrices. Samples were kept isothermal at 100°C for 5 minutes. This was followed by cooling step to -20°C again. Temperature was left isothermal for 2 minutes. Finally a heating step to 300°C was followed to measure the endothermic peak of theophylline if existed. All the heating and cooling sequences were carried out at a rate of 10°C/min.

## **2.9. Thermo Gravimetric Analysis (TGA)**

A thermo gravimetric analysis TGA Q5000 (TA Instruments, Elstree, Hertfordshire, UK) was used to measure the thermal decomposition profiles of the extruded filaments and printed tablets, in addition to the raw materials.

Samples of approximately 5 mg were added to an aluminium pan in the TGA. Samples were heated between 25°C and 600°C with a heating rate of 10°C/min. The data was analysed using TA 2000 analysis software.

## **2.10. *In Vitro* drug release study via pH change USP II dissolution test**

*In vitro* drug release studies for all gastro-resistant coating formulations used in this study were conducted in a USP II dissolution apparatus (AT 7 Smart, SOTAX, Switzerland). Each experiment was carried out in triplicate in dissolution medium at 37±0.5 °C with paddle speed of 50 rpm. The tablets were tested in 750 mL of a stimulated gastric fluid (0.1M HCl, pH 1.2) for 2 h, followed by 16-hour exposure to pH 6.8 phosphate buffer. Within all the experiment the amount of released theophylline was determined at 5 min intervals by UV/VIS spectrophotometer (PG Instruments Limited, UK) at the wavelength of 272 nm and path length of 1 mm. Data was analysed using IDISis software (Automated Lab, 2012).



### 3. Results and discussion

Here we present a strategy for the production of tablets with immediate and extended release properties that allows the using of realistic high loading of drug (50%). The process is schematically illustrated in Fig.1. Firstly, theophylline loaded filaments were produced via processing a physical mixture of drug and polymer through hot-melt extrusion. Computer software is utilized to design a capsule-shaped tablet with different dimensions. The theophylline loaded filaments are utilized as a feed filament for FDM based 3D printer. SEM images of 3D printed tablets showed that tablets are made of staked layers of 200  $\mu\text{m}$  thickness (Fig. 1E). The process takes approximately 5 min and is filmed in Video S1.

When tablets with increasing dimensions has been used to fabricate tablets, a good correlation between the volume and tablet mass was achieved ( $R^2 = 0.9997$ ) Fig. S1. This indicated the potential of this system to maintain efficient control of tablet mass using the newly fabricated filaments adapted filament. The relevant equation was utilized to fabricate tablets with increasing tablet mass as in equation 3. Table 2 and Figure 2 demonstrated the fabrication of different tablets with therapeutic dose of theophylline: 60, 120, 200, 250 and 300mg. The tablets demonstrated a good ecstastic shape and high physical resistance (crushing strength  $>490\text{N}$ ). The accuracy of dose was in the range of 91.34-95.92% with small variation co-efficient in the range of 0.8-3.4%. The printing method demonstrated a high correlation between the target and achieved dose ( $R^2 = 0.9995$ ) (Fig.2B). The *in vitro* drug release pattern for theophylline indicated that drug release occurred mainly through diffusion mechanism. The retrieved dissolution particles indicated the formation of pores due to drug leaching through the system. The larger the tablet, the slower the release pattern. Such a trend has also been demonstrated in previous paper justa.

The choice of printing speed appeared to have significant impact of the external appearance of the tablet and the thickness of deposited layer (Fig. 3A-C). SEM images indicated that low, standard and high printing resolution (which corresponds to faster printing speed) resulted in the formation layer thicknesses of 400, 200 and 100 $\mu\text{m}$  respectively. However, the printing speed appeared not to have significant influence on the variation of tablet weight or pattern of drug release for Eudragit RL based 3D printed tablets (Fig. 3D, E). Also, standard and low resolution took similar printing time while higher resolution appeared to

significant increase the printing time. Such a difference may have major influence when optimizing the printing process to minimize dispensing time while maintaining the quality of the 3D printed tablet.

In order to test the applicability of this method to tailor drug release from 3D printed tablets, different polymer or a mixture of polymers were used in replacement of Eudragit RL. The details of the formulation and preparation method are available in Table 1. Two immediate release polymers (HPC SSL and Eudragit E) were applied. The majority of theophylline release took place within 25 min from both filaments Fig.3A. However, it is obvious in both examples that drug release was slowed down after 3D printing (compared to non-printed filament). This might be attributed to the loss of surface area upon printing. It is also possible that further thermal treatment of drug polymer filament during 3D printing, increased the drug-polymer interaction within polymeric matrix and reduce chances of water imbibition upon introduction to dissolution medium.

To test the possibility of controlling drug release mixtures of Eudragit RL with Eudragit RS or Eudragit E were also investigated (Fig.3 B-C). It was possible to tailor drug release from Eudragit RL filaments with incorporation of less permeable polymer (Eudragit RS). However, the incorporation of Eudragit E appeared to have little influence on drug release from Eudragit RL filament. It was feasible to utilize FDM 3D printing process to print these filaments.

The printed tablets were analysed using thermo-gravimetric analysis in order to compare the thermal decomposition pattern of the printed tablet to that of the extruded filaments and raw materials (Fig. 5A). It was noticed that the pure polymer lost around 3% of its weight up to 110 °C which is believed to be the moisture content of the polymer. The degradation pattern of the physical mixture revealed two degradation steps (Fig. 5B). The first (200 °C) represents the degradation of theophylline while the (340°C) indicated the degradation of the Eudragit RL. It can be noticed that the degradation of the theophylline in the physical mixture is steeper than that of the filament or the tablet which can be related to the distribution and interaction of theophylline particles with the polymeric matrix.

Printed tablets revealed that the Tg of Eudragit has shifted from about 70°C for the pure polymer into about 46°C for the extruded filaments and the printed tablet. The thermal

treatment of the filament through 3D printing appeared to have minimal effect on Tg of the polymer.

These peaks are expected to be for theophylline crystals as the melting point of pure theophylline can be noticed at 272°C. However, the impurity effect of the polymer caused this slight shift in the melting endotherm. The diffraction pattern of tablets containing theophylline revealed diffraction peaks at 7 Å°, 12 Å°, 14 Å° and 24 Å° (Räsänen et al., 2001) that match the diffraction pattern of theophylline. The same diffraction pattern appeared with the extruded filaments from the hot melt extrusion process and in the physical mixture as well as it can be noticed in figure 13. The reduced intensity of the peak suggests that more theophylline is dissolved in the Eudragit RL matrix.

In summary we have reported a new approach for production of flexible dose system based on combined approach of FDM 3D printing and HME. The realistic loading of the tablet, versatile control of dosing and drug release and the finishing quality of the printed tablets

#### **4. Conclusion**

3D printing process proved universal to different methacrylic polymers such as Eudragit RL, Eudragit RS and Eudragit E. It was also possible to print tablets using HPC SSL polymer. The use of HME based pharmaceutical filament preserved the linear relationship between the mass and printed volume and was utilized to effectively control the dose ( $R^2=0.9995$ ) and maintained a dose accuracy of 91-95%. Higher resolution printing quality doubled the printing time but offered little effect on release pattern and weight accuracy. Thermal analysis indicated that a potential amount of theophylline remained in a crystal form in the 3D printed tablet with possible reduction in the crystallinity percentage compared to non-printed filament. This could partially explain their slower drug release pattern in comparison with filaments. Because of the low cost and wide-availability of FDM 3D printers, these 3D printers hold promise for clinical applications.

#### **Acknowledgement**

The authors would like to acknowledge Mrs Rim Arafat for her technical support with 3D Max software.

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**Figure 1** Schematic illustration of the fabrication of 3D-printed controlled release theophylline tablet. (A) physical mixture of drug and polymer is processed through hotmelt extrusion to produce theophylline loaded filaments (B), (C) computer software is utilized to design capsule shaped tablet, (D) the theophylline loaded filament is used as a feed for Fused Deposition Modelling (FDM) based 3D printer, (E) 3D printed tablets produced by standard printing resolution with 200µm layer thickness as shown in SEM images.

**Figure 2** (A) The manipulation of printing scale allows the fabrication of tablet with increasing dose, (b) correlation between the target dose and achieved dose of 3D printed theophylline tablets, (C) In vitro dissolution profile of theophylline from 3D printed tablets with different strength using pH change USP II dissolution test.

**Figure 3** Impact of printing speed (resolution setting) on the morphology and drug release from 3D printed tablets) (A-C) the thickness of the printed layer has been decreased from approximately 400, 200 and 100µm following printing with low, standard and high resolution respectively. The effect of printing speed on D) tablet weight, E) printing time and E) in vitro drug release using pH change USP II dissolution test.

**Figure 4** Impact of FDM based 3D printing on in vitro release of theophylline compared to original filament using (A,B) Immediate release polymers: Eudragit E and HPC SSL, and (C, D) extended release polymers: Eudragit RL and its 1:1 mixtures with Eudragits E and RS.

**Figure 5** Thermal and X-Ray powder Diffraction Eudragit RL based 3D printed tablets. (A) Thermal degradation profile, (B,C) DSC thermograph and X-Ray Powder diffraction spectra of theophylline, Eudragit RL, physical mixture of theophylline and Eudragit RL, Extruded filament of theophylline and Eudragit RL, tablet of theophylline and Eudragit RL.

**Figure 6** Thermal and X-Ray powder diffraction analysis of HPC based 3D printed tablets. (A) Thermal degradation profile, (B,C) DSC thermograph and X-Ray Powder diffraction spectra of theophylline, HPC SSL, physical mixture of theophylline and HPC SSL, Extruded filament of theophylline and HPC SSL, tablet of theophylline and HPC SSL.

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Table 3 Target and actual theophylline dose in 3D printed Eudragit RL based tablets.

## Additional Information

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## References

- Buanz, A.B., Saunders, M.H., Basit, A.W., Gaisford, S., 2011. Preparation of personalized-dose salbutamol sulphate oral films with thermal ink-jet printing. *Pharmaceutical research* 28, 2386-2392.
- Goyanes, A., Buanz, A.B., Basit, A.W., Gaisford, S., 2014a. Fused-filament 3D printing (3DP) for fabrication of tablets. *International journal of pharmaceutics* 476, 88-92.
- Goyanes, A., Buanz, A.B., Hatton, G.B., Gaisford, S., Basit, A.W., 2014b. 3D printing of modified-release aminosalicilate (4-ASA and 5-ASA) tablets. *European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V.*
- Gu, Y., Chen, X., Lee, J.-H., Monteiro, D.A., Wang, H., Lee, W.Y., 2012. Inkjet printed antibiotic- and calcium-eluting bioresorbable nanocomposite micropatterns for orthopedic implants. *Acta Biomater* 8, 424-431.
- Katstra, W.E., Palazzolo, R.D., Rowe, C.W., Giritlioglu, B., Teung, P., Cima, M.J., 2000. Oral dosage forms fabricated by three dimensional printing. *J Control Release* 66, 1-9.
- Khaled, S.A., Burley, J.C., Alexander, M.R., Roberts, C.J., 2014. Desktop 3D printing of controlled release pharmaceutical bilayer tablets. *International journal of pharmaceutics* 461, 105-111.
- Lee, B.K., Yun, Y.H., Choi, J.S., Choi, Y.C., Kim, J.D., Cho, Y.W., 2012. Fabrication of drug-loaded polymer microparticles with arbitrary geometries using a piezoelectric inkjet printing system. *Int J Pharmaceut* 427, 305-310.
- Martin, K.S., McPherson, T.B., Fontane, P.E., Berry, T., Chereson, R., Bilger, R., 2009. Independent Community Pharmacists' Perspectives on Compounding in Contemporary Pharmacy Education. *Am J Pharm Educ* 73.
- Masood, S.H., 2007. Application of fused deposition modelling in controlled drug delivery devices. *Assembly Autom* 27, 215-221.
- Melchels, F.P.W., Feijen, J., Grijpma, D.W., 2010. A review on stereolithography and its applications in biomedical engineering. *Biomaterials* 31, 6121-6130.
- Räsänen, E., Rantanen, J., Jørgensen, A., Karjalainen, M., Paakkari, T., Yliruusi, J., 2001. Novel identification of pseudopolymorphic changes of theophylline during wet granulation using near infrared spectroscopy. *Journal of Pharmaceutical Sciences* 90, 389-396.
- Rattanakit, P., Moulton, S.E., Santiago, K.S., Liawruangrath, S., Wallace, G.G., 2012. Extrusion printed polymer structures: a facile and versatile approach to tailored drug delivery platforms. *Int J Pharm* 422, 254-263.
- Sandler, N., Salmela, I., Fallarero, A., Rosling, A., Khajeheian, M., Kolakovic, R., Genina, N., Nyman, J., Vuorela, P., 2014. Towards fabrication of 3D printed medical devices to prevent biofilm formation. *Int J Pharmaceut* 459, 62-64.
- Skowyra, J., Pietrzak, K., Alhnan, M.A., 2015. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences* 68, 11-17.
- Ursan, I., Chiu, L., Pierce, A., 2013. Three-dimensional drug printing: A structured review. *J Am Pharm Assoc* 53, 136-144.
- website, W.C.M.C., 2014. Study Shows Inconsistent Dosages of Widely Used Eye Disease Drug, <http://weill.cornell.edu/news/pr/2014/09/study-shows-inconsistent-dosages-of-widely-used-eye-disease-drug-szilard-kiss-donald-damico.html>, last accessed 10/2/2015.
- Yu, D.G., Shen, X.X., Branford-White, C., Zhu, L.M., White, K., Yang, X.L., 2009. Novel oral fast-disintegrating drug delivery devices with predefined inner structure fabricated by Three-Dimensional Printing. *The Journal of pharmacy and pharmacology* 61, 323-329.
- Yu, D.G., Yang, X.L., Huang, W.D., Liu, J., Wang, Y.G., Xu, H., 2007. Tablets with material gradients fabricated by three-dimensional printing. *Journal of pharmaceutical sciences* 96, 2446-2456.

**Table 1 Processing parameters for filament production using HME and subsequent 3D printing**

Formulation (Weight ratio)	HME process		3D Printing process	
	Initial temperature (°C)	Extruding temperature (°C)	Extruding temperature (°C)	Platform temperature (°C)
Eudragit RL/Theophylline/TEC 45/50/5	130	120	170	90
Eudragit RS/ Theophylline /TEC 42.5/50/7.5	130	110	150	60
Eudragit E/ Theophylline /TEC 46.5/50/3.5	130	110	140	60
Eudragit RL/Eudragit E/ Theophylline /TEC 22.5/22.5/50/5	130	115	140	90
Eudragit RL/Eudragit RS/ Theophylline /TEC 22.5/22.5/50/5	130	120	150	90
HPC SSL/ Theophylline /Triacetin 46/50/4	125	110	160	20

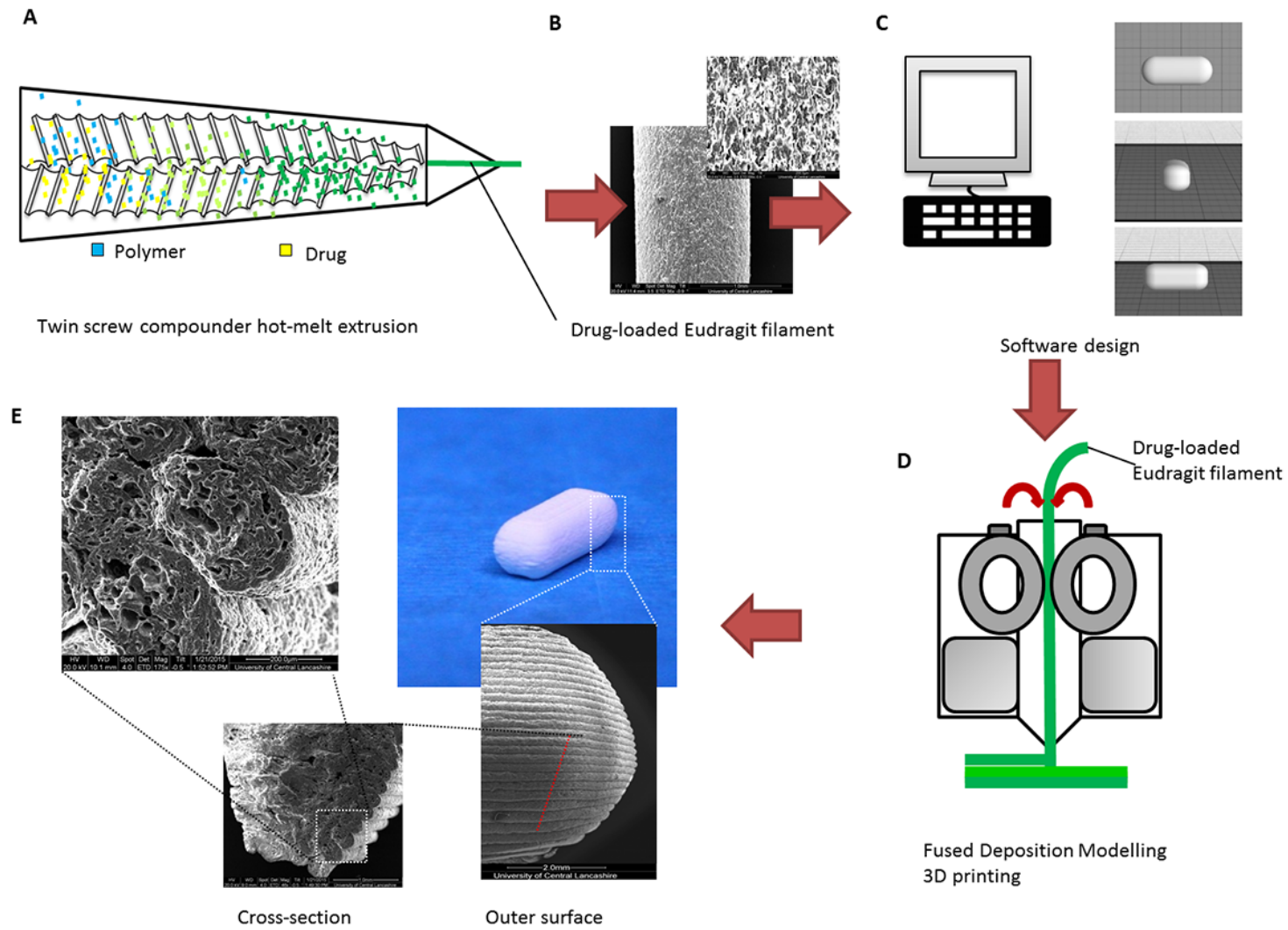
**Table 2 Target and actual tablet mass, volume and dimensions.**

<b>Expected tablet mass (mg)</b>	<b>Volume (mm<sup>3</sup>)</b>	<b>Dimensions (mm)</b> X x Y x Z	<b>Average tablet mass ±SD (mg)</b>	<b>Weight accuracy ±SD (%)</b>
<b>150</b>	210.14	11.34 x 4.13 x 4.49	149.77±3.15	99.84±2.10
<b>300</b>	420.27	14.29 x 5.20 x 5.66	300.53±4.23	100.18±1.41
<b>450</b>	630.42	16.35 x 5.95 x 6.48	455.17±1.84	101.15±0.41
<b>600</b>	840.55	18.00 x 6.55 x 7.13	613.43±4.69	102.24±0.78
<b>750</b>	1050.69	19.39 x 7.06 x 7.68	774.43±8.71	103.26±1.16

**Table 3 Target and actual theophylline dose in 3D printed Eudragit RL based tablets.**

<b>Target dose (mg)</b>	<b>Tablet mass<math>\pm</math> SD (mg)</b>	<b>Theoretical dose <math>\pm</math>SD (mg)</b>	<b>Achieved dose <math>\pm</math>SD (mg)</b>	<b>Dose accuracy <math>\pm</math>SD (%)</b>
<b>60</b>	123.0 $\pm$ 1.1	61.5 $\pm$ 0.57	58.8 $\pm$ 0.8	95.56 $\pm$ 2.03
<b>125</b>	253.7 $\pm$ 4.5	126.9 $\pm$ 2.26	121.7 $\pm$ 2.3	95.92 $\pm$ 0.80
<b>200</b>	411.2 $\pm$ 5.9	205.6 $\pm$ 2.97	192.4 $\pm$ 4.0	93.62 $\pm$ 3.39
<b>250</b>	516.6 $\pm$ 10.7	258.3 $\pm$ 5.35	237.1 $\pm$ 1.3	91.83 $\pm$ 2.63
<b>300</b>	618.9 $\pm$ 6.3	309.5 $\pm$ 3.13	282.6 $\pm$ 3.0	0 $\pm$ 2.01



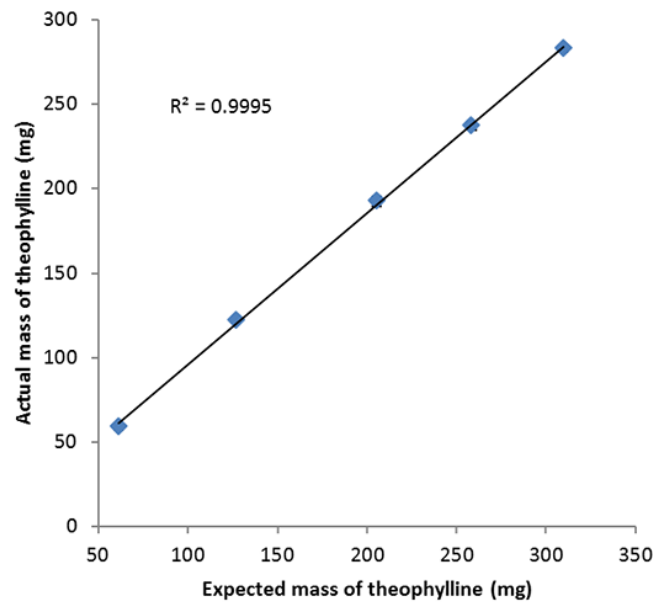


**A**



3D printed theophylline tablets with increased strength

**B**



**C**

